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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,240	07/01/2003	Li-Xi Yang	056367-0200	3322

38706 7590 07/18/2007

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
07/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,240	YANG, LI-XI	
	Examiner	Art Unit	
	Nizal S. Chandrakumar	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06.04.2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,13,22-24 and 57-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,13,22-24 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was filed 07/01/2003.

Applicants' response filed 06/04/2007 to office action filed 03/05/2007 is acknowledged.

Claims 1,8, 13-15, 22-24 and 57-59 were pending.

Applicants amended claims 1 and cancelled claims 14 and 15.

Claims 1, 8, 13, 22-24 and 57-59 are pending.

The indicated allowability of claims 13 and 57-59 in the office action filed 03/05/2007 is withdrawn for the following reasons.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 & 22-24 and claims 13 & 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the efficacy of one of the compounds, does not reasonably provide enablement for wide number of structures claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification is enabling assessment of in vitro efficacy of a few compounds but is not correlating the in vitro efficacy with in vivo toxicity or efficacy. The specification is enabling for therapeutic efficacy of one specific compound of formula of claim 1, namely podophylotoxin-4-O-ester of thymine-1-acetic acid (compound 0003061, Table 1) corresponding to the formula wherein m = 1 and R1 is unsubstituted thymin-1-yl. However, the formula encompasses

structures in which m is 0 to 10 and R1 is optionally substituted pyridine-3-yl or optionally substituted thymin-1-yl.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims,
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The invention related to allegedly novel derivatives of podophyllotoxin that are useful for treating various types of cancer.

The state of the prior art: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects the observed activity of one of the derivatives of a core structure is not predictive of another derivative of the

same core structure. Hence, in the absence of a showing that any derivative of podophyllotoxin of the said formula could be efficacious anticancer compound, one of ordinary skill in the art is unable to fully predict possible results from the administration of any compound of claim 1 due to the unpredictability of the effects of substitution on the heterocyclic modification (i.e., R1) and or modification of linker chain length (i.e. m). Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit

characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The presence or absence of working examples: The working examples of the specification are for the determination of in vitro efficacy of test compounds. The specification also provides one method each for assessing the toxicity and efficacy of test compounds in mouse models. Table in page 51 provides data for several compounds for in the in vitro assay. The specification contains toxicity or efficacy information for only one specific compound (0003061).

The amount of direction or guidance present: The guidance present in the specification is that of the compounds that are tested that some work, some don't work, and some work to a weak extent. Even in the in vitro situations, very similar compounds have been shown to have one work well and the other have no effect at a given drug concentration (see Table on page 51). The specification states that a variety of derivatives of podophyllotoxin of the said formula are useful for treating various types of cancer. The specification shows that only one of the several possible compounds of the formula show efficacy in the above-mentioned mouse model.

The breadth of the claims: The claims are drawn to the treatment of various types of cancer with compounds of formula of claim 1.

The quantity of experimentation needed: The quantity of experimentation needed is undue. One skilled in the art would need to determine particulars of substitution on the R1 group and what linker length m that are needed in a compound of formula would provide a compound with acceptable toxicity and efficacy. This would require preparing the various possibilities of the variable m and R1 and further determining by trial and error methods to determine which of the substitution on R1 that would provide compounds with desirable activity.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad claims of the compound for treatment of various types of cancer. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8, and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potier et al. (FR 2837824, priority date 03.28.2002).

The prior art relates to podophyllotoxin derivatives made by the esterification of hydroxyl group of podophyllotoxin with various carboxylic acids. The carboxylic acids contain optionally substituted aryl and heteroaryl groups. These derivatives are alleged to have cytotoxic activity.

The difference between the prior art and the claims at issue is that the instant case the said carboxylic acids contain pyridine-3-yl, thymin-yl, or furanyl groups while the prior art contain generically claimed heteroaryl group. That is, the instantly claimed heterocyclic pyridine compounds are positional isomers *(vide infra)* of the compounds of the prior art.

Positional isomers *(vide supra),* having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry.

One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial ester derivatives of podophyllotoxin, which would have useful anticancer properties. The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art. A strong case of *prima facie* obviousness has been established.

Claims 13 and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (Yaoxue Xuebao 1997, 32(12), 898-901).

The prior art relates to podophyllotoxin derivatives made by the esterification of hydroxyl group of podophyllotoxin with various carboxylic acids. The carboxylic acids contain substituted or unsubstituted furanyl group. The compounds allegedly showed significant antitumor activities.

The difference between the prior art and the claims at issue is that the instant case the said furanyl carboxylic acids are not 5-nitro-furanyl carboxylic acids.

The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these nitro substituted analogs based on the expectation that such close analogues would have

similar properties and upon the routine nature of such analog design experimentation in the art of medicinal chemistry.

One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial ester derivatives of podophyllotoxin, which would have useful anticancer properties. The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art. A strong case of *prima facie* obviousness has been established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 and dependent claims are rejected under 35 U.S.C. 102(b) as being anticipated by Potier et al. (FR 2837824, priority date 03.28.2002).

Potier et al. teach (page 19, compound No. 15), corresponding to compound of formula of claim 1 wherein R1 is pyrin-3-yl, X is a covalent bond and m is 2.

No claims are allowed.

Previously presented Rejections:

Applicants' amendment to the claims overcome the Claim Rejections – 35 USC § 112 set forth in the previous action filed 06/04/2007.

Response to Applicants Remarks:

Applicants request the reconsideration of the application in view of the amendments. The application was reexamined.

Conclusion

Applicant's amendments overcome part of the rejections set forth in the office action filed 06/04/2007. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative

D. MARGARET SEAMAN
PRIMARY EXAMINER